Racial Differences in Response to EFV-Containing vs. LPV/r-Containing Regimens

Guest JL, Ataher QS, Rimland D
Atlanta VA Medical Center and Emory University, Atlanta, GA.

Updated Abstract

Objective: To examine potential differences in virologic or immunologic response to highly active antiretroviral therapy (HAART) between African-American and Caucasian HIV/AIDS patients.

Methods: 631 HIV/AIDS patients at the Atlanta Veterans Affairs Medical Center (AVAMC) receiving either lopinavir/ritonavir (LPV/r) or efavirenz (EFV)-containing regimens for at least one month were included. For patients receiving these drugs sequentially, response to only the first regimen was studied. Patients starting both drugs in the same regimen were excluded. Patients were censored after stopping the regimen. Virologic failure (VF) was defined as 2 consecutive HIV RNA values >400 copies/mL after 2 months of initiating HAART. Immunologic failure (IF): defined as a decrease in CD4+ cell count after an initial response of a CD4+ cell count of >50 cells/mm^3 above baseline. Race was defined as either African-American (AA) or Caucasian. No other racial groups were represented. Multivariate survival analyses were performed to determine the independent association between outcomes (VF & IF) and race controlling for age at baseline, HIV risk factor, baseline and nadir CD4+ cell count, baseline HIV RNA level, number of prior antiretroviral regimens, AIDS defining illness, hepatitis C seropositivity and date of HIV diagnosis.

Results: In a multivariate Cox model including LPV/r and EFV patients, race was a significant predictor of IF (hazard ratio [HR]: 0.64, 95% CI: 0.45-0.91; AA race protective) but not of VF (HR: 0.85, 95% CI: 0.59-1.23). For EFV patients, race was again a significant predictor of IF (HR: 0.63, 95% CI: 0.43-0.92) but not of VF (HR: 0.92, 95% CI: 0.62-1.38). For LPV/r patients, race was not a significant predictor of IF (HR: 0.26, 95% CI: 0.05-1.27) or VF (HR: 0.73, 95% CI: 0.14-3.88); however, this may be due in large part to the small sample size evaluated in this study.

Conclusion: Race appears to be associated with IF to EFV, while a clinical trend was observed with respect to LPV/r. VF did not differ by race while on EFV or LPV/r. In this population with equivalent access to medical care and antiretroviral agents, genetic factors may have contributed to the differences in IF.

Background

- Use of HAART has significantly improved the prognosis of HIV infection.
- Effectiveness may vary in different demographic groups with varied risk factors.
- The mortality rate for African American patients with AIDS is approximately 50% higher than that for Caucasian patients with AIDS.[1]
- Multiple studies have found a negative association of non-white race with antiretroviral use.[2]
- It has not been determined if pharmacokinetic, immunologic or genetic differences by race/ethnicity influence the response to a particular antiretroviral regimen.
- A study of Danish HIV patients found no major role of race and ethnic origin in the virological, immunologic or clinical response to HAART if access to health care is free.[3]
- Patients treated at the Atlanta VA medical center have equal access to medical care and antiretroviral therapy.

Objective/Study Purpose

To examine potential differences in virologic or immunologic response to highly active antiretroviral therapy (HAART), including by class, between African-American and Caucasian HIV/AIDS patients.

Methods

- Patients:
  - HIV/AIDS patients at the Atlanta Veterans Affairs Medical Center (AVAMC) receiving either lopinavir/ritonavir (LPV/r) (n=86) or efavirenz (EFV) (n=545) for at least one month
- Data collection: abstracted from HIV Atlanta VA Cohort Study (HAVACS) database and the AVAMC pharmacy, laboratory and the Computerized Patient Record System (CPRS) databases
- Outcomes:
  - Virologic failure (VF): defined as 2 consecutive HIV RNA values >400 copies/mL after 2 months of starting HAART
  - Immunologic failure (IF): defined as a decrease in CD4+ cell count after an initial response of a CD4+ cell count of >50 cells/mm^3 above baseline
- Exposure of interest: Race, defined as either African-American (AA) or Caucasian

- Covariates: age at baseline, HIV risk factor, baseline and nadir CD4+ cell count, baseline HIV RNA level, number of prior antiretroviral regimens, AIDS-defining illness, hepatitis C seropositivity, and date of HIV diagnosis
- Censoring: at end of study regimen
- Statistical analyses:
  - Univariate analyses generating Kaplan-Meier (KM) survival curves to analyze associations between the outcomes (VF and IF) and race, while adjusting for the potential confounders (see Covariates)
  - Multivariate survival analyses using the Cox proportional hazards model

Results

- AA patients had lower nadir CD4+ cell count and were younger at start of the regimen under study than the Caucasian patients regardless of ARV regimen. More Caucasians appear to have been infected through sexual contact (Men who have sex with men [MSM]), while more African Americans appear to have been infected during injection drug use (IDU) (Table 1).

- Among patients receiving an EFV-containing regimen, AA patients had lower baseline CD4+ cell count and higher prevalence of Hepatitis C virus infection and opportunistic infections than the Caucasian patients. These differences were not seen in the LPV/r group (Table 1).

- There was no apparent difference by race with respect to the proportion of subjects experiencing VF or in the time to VF, either in the study group as a whole or by specific drug (Table 2, Figures 1-2).

- Higher baseline viral load was an independent statistically significant predictor of time to VF for the study group as a whole as well as for patients on either EFV or LPV/r ($p < 0.05$ for all) (Table 2).

- Baseline CD4+ cell count was a significant predictor of VF in the LPV/r group but not in the EFV group (Table 2).

- Longer duration of the regimen under study was an independent predictor of VF for the EFV group but not for the LPV/r group ($p<0.0001$; Table 2). For the EFV group, longer duration of this regimen conferred protection against VF during follow-up while the opposite trend was seen with the LPV/r patients. However, this association in LPV/r group was not statistically significant with a wide confidence interval suggesting a lack of statistical power.

- AA patients taking EFV were 37% less likely to experience IF during follow up than were Caucasian patients ($p=0.0179$) after controlling for other important covariates such as number of previous ART regimens, age at baseline, year of HIV diagnosis etc (Table 3, Figure 4).

- Longer duration of the regimen under study was an independent predictor of longer time to IF in both the EFV and LPV/r groups (Table 3).

- A trend was seen with AA patients taking LPV/r being less likely than Caucasian patients to experience IF during follow up (Table 3, Figure 3). However, this result did not reach statistical significance, due in large part to the small sample size evaluated in this study (Figure 5).

Conclusions

Race appears to be associated with the time to immunologic failure in patients who received EFV, while a clinical trend was observed with respect to LPV/r, with AA patients experiencing less immunologic failure during follow up. Virologic failure did not differ by race while on EFV or LPV/r. In this population with equivalent access to medical care and antiretroviral agents, genetic factors may have contributed to the differences seen in the rates of immunologic failure.

References

1. Centers for Disease Control and Prevention. U.S. HIV and AIDS cases reported through December 2001. HIV/AIDS Surveill Rep 2001;13:1-41.

2. Palacio H, Kahn JG, Richards TA, Morin SF. Effect of race and/or ethnicity in use of antiretrovirals and prophylaxis for opportunistic infection: a review of the literature. Public Health Rep 2002;117(3):233-51.

3. Jensen-Fangel S, Pederson L, Pederson C, Larsen CS, Tauris P, Moller A, Sorensen HT, Obel N. The effect of race/ethnicity on the outcome of highly active antiretroviral therapy for human immunodeficiency virus type 1-infected patients. Clin Infect Dis 2002; 35(12):1541-8.

Table 1. Clinical, Treatment and Laboratory Parameters by Antiretroviral Class and Race

	EFV			LPV/r		
	Caucasian (N=174)	**AA (N=371)**	**p-value**	**Caucasian (N=25)**	**AA (N=61)**	**p-value**
Number of previous ART regimens (%):						
0-1	101 (58)	242 (65)	0.18[a]	11 (44)	29 (48)	0.69[a]
2-4	66 (38)	121 (33)		13 (52)	27 (44)	
>4	7 (4)	8 (2)		1 (4)	5 (8)	
HCV infected (%)	19 (12)	110 (31)	**<0.0001**[a]	4 (17)	14 (27)	0.37[a]
HIV Risk Factor:						
Men who have sex with men (MSM)	124 (72)	174 (47)	**<0.0001**[a]	18 (72)	33 (54)	**0.03**[a]
Injection drug user (IDU)	8 (4)	71 (19)		0 (0)	14 (23)	
Unknown/Other	41 (24)	126 (34)		7 (28)	14 (23)	
Opportunistic infection (%)	38 (29)	61 (20)	**0.04**[b]	4 (18)	10 (19)	0.25[b]
Baseline viral load (log_{10} copies/ml), Mean (range)	113,911 (104-689,157)	119,936 (61-749,714)	0.73[c]	122,460 (896-646,787)	217,703 (563-624,902)	0.15[c]
Baseline CD4+ count (cells/mm^3), Mean (range)	307 (2-1,673)	240 (0-2,312)	**0.0091**[c]	274 (11-1,193)	214 (1-712)	0.49[c]
Nadir CD4+ count (cells/mm^3), Mean (range)	168 (0-745)	111 (0-623)	**0.002**[c]	127 (2-333)	84 (1-500)	0.07[c]
Age at treatment initiation, Mean (range)	44 (24-72)	42 (23-74)	**0.04**[c]	48 (35-73)	42 (29-57)	**0.009**[c]
Duration of regimen under study for virologic event, Mean (range)	23.04 (1-88)	19.17 (1-61)	**0.048**[c]	21.56 (1-56)	15.85 (1-34)	0.1345[c]
Duration of regimen under study for immunologic event, Mean (range)	19.78 (1-59)	18.50 (1-61)	**0.51**[c]	20.52 (3-35)	14.34 (1-33)	0.0594

a: Chi-square test
b : Fisher's exact test
c: Two sample t-test

Table 2. Time to Virologic Failure: Results from Cox Proportional Hazard Model

	All patients*		EFV treated group*		LPV/r treated group*	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
African American race	0.85 (0.59-1.23)	0.39	0.92 (0.62-1.38)	0.69	0.73 (0.14-3.88)	0.7123
Higher baseline viral load	1.4 (1.18-1.7)	**0.0002**	1.34 (1.11-1.63)	**0.0026**	3.73 (1.66-8.39)	**0.0014**
Longer duration of regimen under study	0.36 (0.25-0.52)	**<0.0001**	0.33 (0.22-0.48)	**<0.0001**	6.78 (0.83-55.16)	0.0735
Longer duration of HIV disease	1.13 (0.92-1.39)	0.24	1.24 (1.00-1.54)	**0.0491**	0.194 (0.06-0.68)	**0.0106**
Lower baseline CD4+ cell count	0.96 (0.77-1.2)	0.75	0.96 (0.75-1.23)	0.7591	0.11 (0.02-0.59)	**0.0106**

*Non-significant variables included in the model: antiretroviral regimen under study, diagnosis of AIDS by opportunistic infection, hepatitis C virus infection, HIV risk factor, number of previous antiretroviral regimens, nadir CD4 count

Table 3. Time to Immunologic Failure: Results from Cox Proportional Hazard Model

	All patients*		EFV treated group*		LPV/r treated group*	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
African American race	0.64 (0.45-0.91)	**0.0135**	0.63 (0.43-0.92)	**0.0179**	0.26 (0.05-1.27)	0.0969
Higher baseline viral load	0.86 (0.74-1.00)	0.0594	0.86 (0.73-1.02)	0.0788	0.905 (0.52-1.58)	0.7269
Longer duration of regimen under study	0.61 (0.47-0.78)	**0.0001**	0.62 (0.47-0.81)	**0.0004**	0.26 (0.07-0.96)	**0.0433**
Longer duration of HIV disease	1.04 (0.86-1.26)	0.6650	1.02 (0.83-1.24)	0.8608	2.16 (0.71-6.58)	0.1748
Lower baseline CD4+ cell count	0.83 (0.67-1.01)	0.0688	0.85 (0.68-1.05)	0.1354	0.46 (0.15-1.43)	0.1805

*Non-significant variables included in the model: antiretroviral regimen under study, diagnosis of AIDS by opportunistic infection, hepatitis C virus infection, HIV risk factor, number of previous antiretroviral regimens, nadir CD4 count

Figure 1. Proportion of Patients with Virologic Failure in Different Races by Treatment Groups

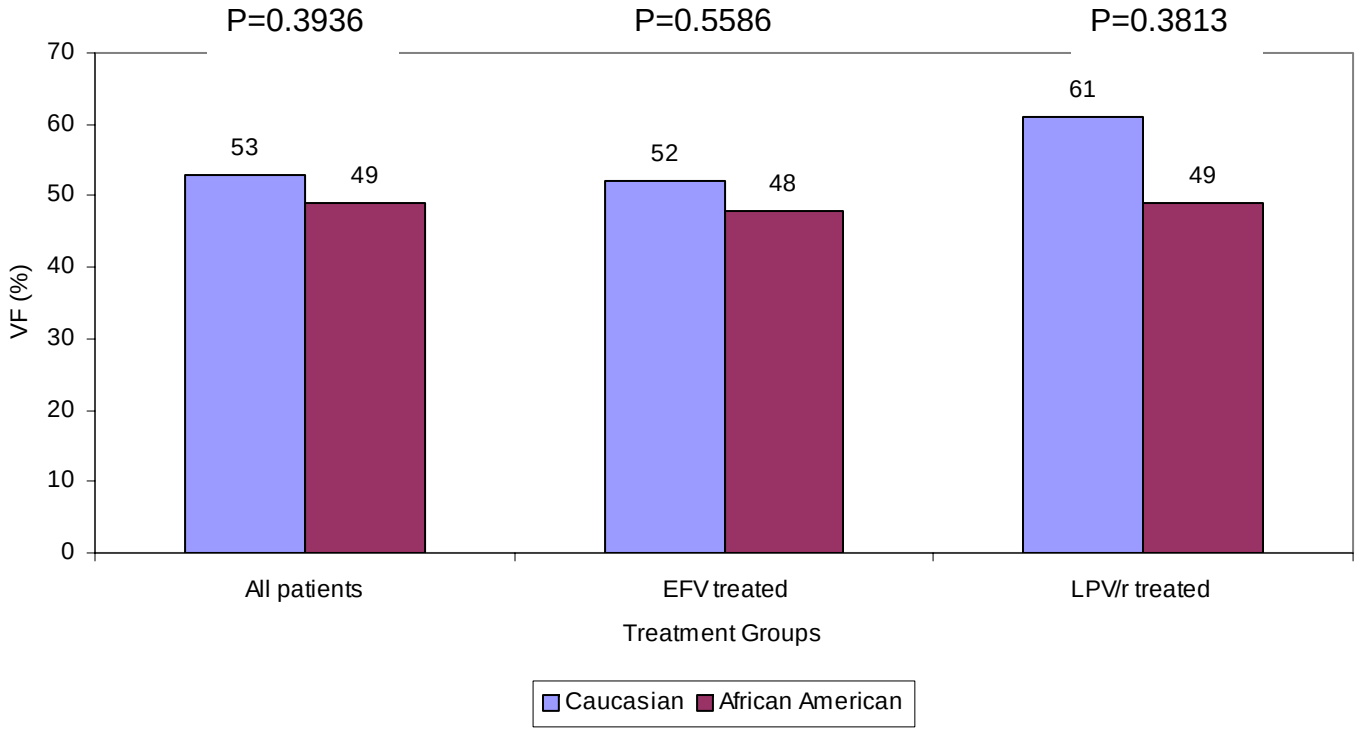

Figure 2. KM curves for VF stratified on race
All Patients

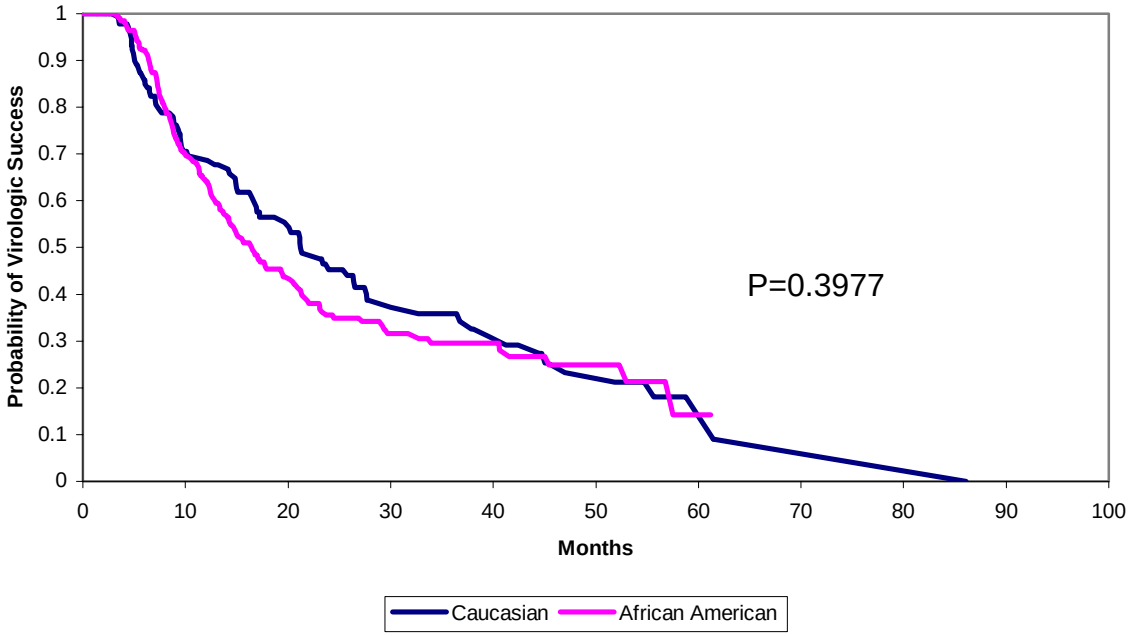

Figure 3. Proportion of Patients with Immunologic Failure In Different Races by Treatment Groups

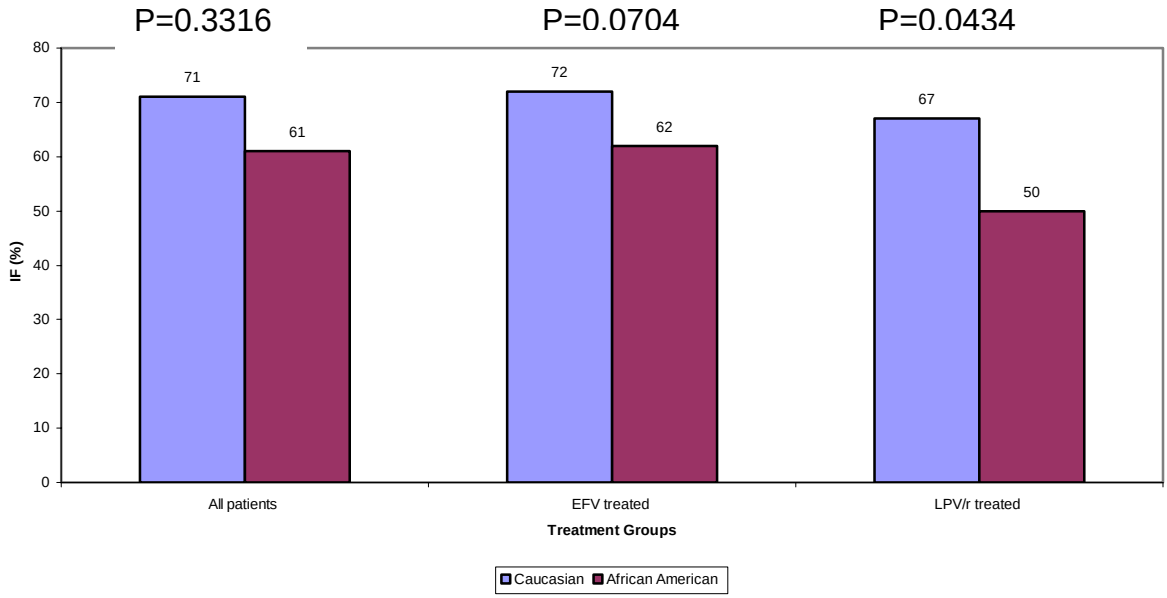

Figure 4. KM Curves for IF Stratified on Race
Patients Receiving EFV

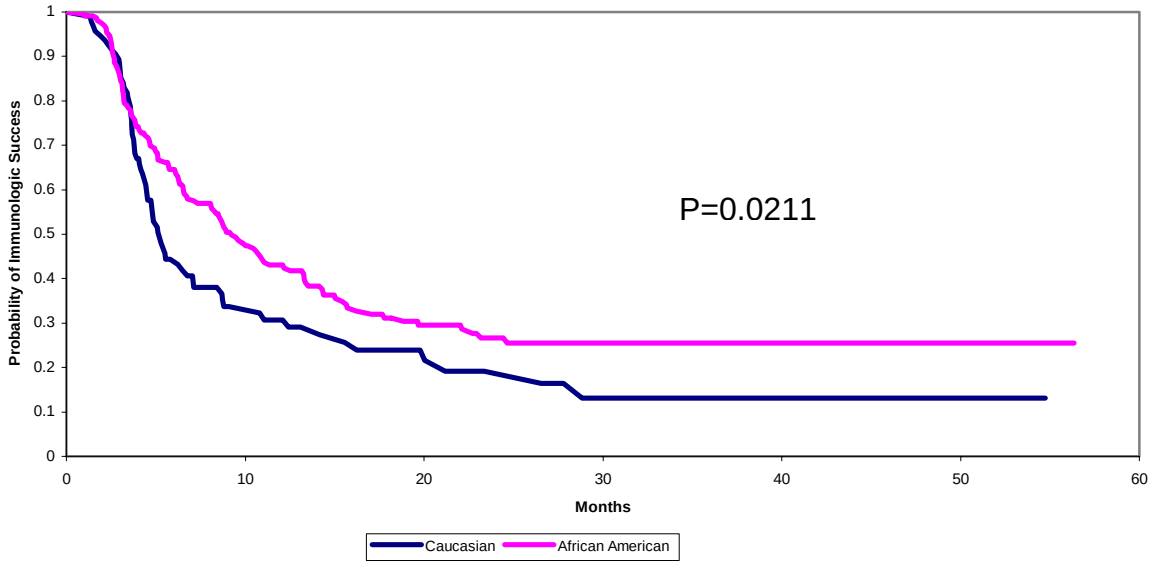

Figure 5. KM Curves for IF Stratified on Race
Patients Receiving LPV/r